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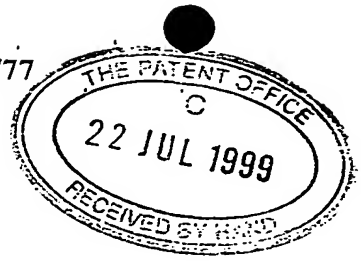

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Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your Reference — MA/PI3746

2. Patent application number *(The Patent office will fill in this part)* — 22 JUL 1999 — **9917290.0**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO WELLCOME SPA
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37100 VERONA
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Patents ADP number *(if you know it)* 7044927001

If the applicant is a corporate body, give the country/state of its corporation

4. Title of the invention — PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you know one)*

MICHAEL ATKINSON
(SEE CONTINUATION SHEET)

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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GLAXO WELLCOME HOUSE, BERKELEY AVENUE
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UB6 ONN, GB

Patents ADP number *(if you know it)* 7182629001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

YES

note (d))

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Continuation sheets of this form	1
Description	6
Claim(s)	2
Abstract	-
Drawing(s)	2 + 2

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature Michael Atkinson **22 July 1999**

AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

Kim Allen

0181-966 5721

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Pharmaceutical composition

The present invention relates to a transdermal therapeutic system for the therapeutic administration of diethyl (E) –4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (Lacidipine) to a process for it preparation and to its use in medicine.

Lacidipine, which is described in British patent no. 2164336, is a potent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may also be useful for the treatment of other cardiovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Transdermal drug delivery systems provide a means for obtaining a high degree of control of drug concentration in the blood over a specified time period. Many systems have been developed and used to deliver drugs transdermally. It is however widely recognised that in general it is not possible to predict which particular systems will provide a satisfactory delivery system with a specific drug substance if that has not previously been adminstered by that route.

We have now found that Lacidipine may be advantageously administered transdermally from a drug reservoir containing a solution comprising of lacidipine and at least one skin permeation enhancer.

Thus in one aspect the present invention provides a therapeutic transdermal system (hereinafter TTS) for administering lacidipine which comprises (a) a backing layer, which defines the upper surface of the device (b) a drug reservoir containing a solution comprising lacidipine and at least one skin permeation enhancer, (c) a membrane to control the release of the active ingredient, (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

In a further aspect the present invention provides for the use of lacidipine for the manufacture of a TTS for administration of lacidipine through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

In a preferred embodiment, the present invention provides a TTS for administering lacidipine in the form of skin patch.

Figure 1 of the accompanying drawings gives a schematic section of a transdermal therapeutic system according to the invention.
Figure 2 of the accompanying drawings gives a top view of a transdermal therapeutic system according to the invention prior to fill and sealing.

For a therapeutic transdermal system according to the invention the backing layer (1) is preferably made of a sheet or a film of a flexible material that is substantially impermeable to the lacidipine solution. The layer is preferably of the order of 50 – 200 μm in thickness and may be optionally pigmented. Conveniently the backing layer (1) is heat sealable to the control membrane (3).

The layer (I) is preferably of a material that permits the device to follow the contours of the skin and be worn comfortably on areas of the skin such as joints of flexure.
Examples of flexible polymers useful for the backing layer include polyethylene, polypropylene, polyesters and the like, which may be provided as films or laminates.
A preferred flexible polymer is a laminate consisting of pigmented polyethylene aluminium vapour coated polyester and a medium density polyethylene or ethylene vinyl acetate heat seal layer available from 3M™ under the trade mark Scotchpack ™1006.

The solution comprising lacidipine and at least one skin permeation enhancer may be in a liquid, semisolid or thixotropic form and is contained within the drug reservoir (2).

A suitable amount of lacidipine present in the solution is within the range 1 – 20% e.g. 1 - 10% by weight of the total solution.

Examples of suitable solvents for preparing the lacidipine solution include an alkanol e.g. ethanol, propanol or isopropanol or N-methyl-2-pyrrolidinone or mixtures thereof e.g. ethanol and N-methyl-2-pyrrolidinone.

Example of suitable skin permeation enhancers of this invention include saturated and unsaturated fatty acid esters, alcohols such as ethanol, propanol, isopropanol, n-decyl alcohol, etc, pyrrolidone derivatives (i.e. N.methyl-2-pyrrolidone) or (+)1-Methyl-4-(1-methylethenyl)cyclohexene: ((+) limonene).

Conveniently fatty acid ester enhancers include esters of carboxylic acids containing from C_8 to C_{16} carbon atoms. Preferred are those esters derived from palmitic acid, steric acid or lauric acid.
Conveniently fatty acid esters for use in the invention include fatty acid esters polyhydroxy alcohols such as sorbitol, glycerol or propylenglycol.
Particularly preferred are fatty acids esters include those derived from sorbitol and of those sorbitan palmitate (Span™40) is particularly preferred.
Use of combinations of two or more of the skin permeation enhancer compounds may frequently result in superior results, such as greater transdermal absorption.
Thus it has been found that a mixture of ethanol, N-methyl-2-pyrrolidone and sorbitan palmitate (Span™ 40) is a preferred skin permeation enhancing mixture.
The amount of ethanol present is conveniently within the range 10-60% e.g. 30-40% by weight of the total reservoir solution. The amount of Span™ 40 is conveniently within the range 0.5-6.0% e.g. 1-5% of the total reservoir solution.
The amount of N-methyl-2-pyrrolidone present is conveniently within the range 20-70% e.g. 40-70% by weight of the total reservoir solution.
A particularly preferred reservoir solution of the invention contains 3-5% e.g. 4% of lacidipine, 30-40% e.g. 36.5% of ethanol, 3 to 5% e.g. 3.5% of Span™ 40, and 50-60% e.g. 56% of N methyl-2-pyrrolidone by weight of the total solution.

The solution comprising lacidipine with one or more skin permeation enhancers forms a further aspect of the invention. This solution may be prepared by dissolving the lacidipine in a solution of the enhancers and the solvents using conventional procedures.

The membrane (3) to control the release of the lacidipine is a thin, flexible uniformly microporous, flat sheet membrane which provides a constant rate of drug release independent of time or of the amount of the active ingredient that remains in the reservoir. A preferred membrane is a flat sheet membrane made from food grade polypropylene and polyethylene resins known under the Trade Mark Celgard™ 2400 or Celgard™ 2500, available from Hoechst Celanese. Celgard™ 2400 is the preferred membrane. Other suitable membranes include a microporus polyethylene membrane Solupor™ or an EVA membrane e.g. Co Tran™.

The contact adhesive layer (4) is a pressure sensitive adhesive suitable for long term skin contact. It must also be physically and chemically compatible with lacidipine and the vehicles employed. Further active ingredients must be soluble in the adhesive, so that the drug does not partition into the backing layer, but will partition into the skin. Conveniently the contact adhesive layer also adheres to the membrane (3).

Suitable adhesives include silicones, polyisobutylenes, polyacrilates, polyuretanes, plasticized ethylene, vinylacetate co-polymers, polystirene-isoprene copolymer and a mixture thereof. Presently preferred contact adhesives are polyacrylates, silicones and polyurethanes.
Particularly preferred are the amine resistant silicone based pressure sensitive adhesives such as BIO-PSA Q7-4301, available from the Dow Corning Corp.

The release liner (5) is a disposable element which serves only to protect the adhesive layer prior to application to the skin.
Typically, the release liner is formed from a material impermeable to the drug, vehicle, and adhesives and which is easily stripped from the contact adhesive. Release liners are typically treated with silicone or fluorocarbons.

A fluoro coated polyester film under the Trade Mark Scotchpatch™ 1022 available from 3M is particularly preferred.

In a further aspect of the invention provides a method for administering lacidipine to a pre-determined area of intact skin, over defined time period and at an administration rate to reach and maintain an effective therapeutic dose of lacidipine for the control of hypertension and other cardiovascular diseases. In order to reach the effective blood levels of the drug a preferred rate of administration is between 0.1 to 2 μg/hr, more preferably in the range of 0.4 to 0.6 μg/hr, through a skin area of 2.0 to 90 cm^2, more preferably 10 to 40 cm^2. The amount of the drug delivered into the skin may be controlled by a number of factors, including skin patch size, degree of initial drug loading, the choice of skin permeation enhancers and the control release membrane.

The efficacy of the transdermal therapeutic system to deliver the lacidipine at the required rate and over the required time scale can be determined using conventional in vitro and in vivo test procedures. Thus for example using the in vitro procedure that is described by Franz J. T. Journal of Investigative Dermatology 64(3) 190-5 1975.

The present invention also provides a process for the production of the transdermal therapeutic system according to the invention which comprises the following steps:

a) coating the release liner (5) with the adhesive layer (4) which is then laminated with the control membrane (3);

b) securing the backing layer (1) to the control membrane (3) by means of a seal (7) so as to obtain the sachet (8) having an opening (6);

c) filling the reservoir (2) in the sachet (8) via the opening (6) with a solution comprising lacidipine and at least one skin permeation enhancer and then sealing the opening (6);

In the preparation of the open reservoir sachet (8) it is convenient to use the backing layer (1) and the laminate comprising members (3), (4) and (5) in sheet form and when the said backing layer is sealed to the said laminate then the

sachet (8) of the desired size and shape can be stamped or punched out either simultaneously with its formation or in a subsequent operation.

The individual TTS can be sealed into an appropriate packaging material using standard methods in the art.

A convenient packaging material for use comprises a laminate of paper, polymer (i.e. polyethylene) and aluminium film.

An example of a suitable means to seal the individual TTS into the appropriate packaging material is a polyethylene polymer available from Du Pont and known under Trade Mark Surlyn™

The example presented below serves to illustrate the invention without in any way limiting its scope:

Example 1

a)Preparation of the reservoir solution containing lacidipine – Dose per patch

N-methyl pyrrolidone(1.12g) and sorbitan palmitate (Span™ 40)(0.07g) were added to ethanol (0.737g) and the solution obtained was stirred for about 30'. Lacidipine (80mg) was then added under stirring to obtain a homogeneous solution.

b)Preparation of the Therapeutic Transdermal System (TTS)

A solution of the silicone adhesive (4) [BIO-PSA Q7-4301: silicone resin, amine resistant, high tack 200g/cm^2] was coated onto the release liner (5) [Scotchpak® 1022] . The control membrane (3) (Celgard® 2400) was then laminated to the dried adhesive layer. The backing layer (1) (Scotchpak® 1006) was then secured to the control membrane with a heat seal (7) to form a sachet (8) having a drug reservoir (2) connected to an opening (6). The drug reservoir (2) is then filled with the solution comprising lacidipine and at least one skin permeation enhancer via the opening (6) which is then heat sealed.

Claims

1. A therapeutic transdermal system for administering lacidipine which comprises (a) a backing layer, which defines the upper surface of the device, (b) a drug reservoir containing a solution comprising lacidipine and at least one skin permeation enhancer, (c) a membrane to control the release of the active ingredient, (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

2. A therapeutic transdermal system as claimed in claim 1 wherein the solution in the drug reservoir comprises lacidipine, ethanol, N-methyl-2-pyrrolidinone and sorbitan palminate (Span™ 40).

3. A therapeutic transdermal system as claimed in claim 2 wherein the solution comprises lacidipine 3-5%, ethanol, 30-40%, sorbitan palmitate 3-5% and N-methyl-2-pyrrolidinone 50-60% by weight of the total solution.

4. A therapeutic transdermal system as claimed in any of claims 1 to 3 in the form of skin patch.

5. A therapeutic transdermal system essentially as described in the Example.

6. The use of lacidipine for the manufacture of a therapeutic transdermal system as claimed in any of claims 1 to 5 for administration of lacidipine through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

7. A method for administering lacidipine through a pre-determined area of intact skin and at an administration rate such as to reach and maintain an effective therapeutic dose of lacidipine for the control of hypertension and other cardiovascular diseases which comprises applying to the skin a therapeutic transdermal system as claimed in any of claims 1 to 5.

8. A solution which is suitable for use in a therapeutic transdermal system as claimed in any of claims 1 to 5 which comprises lacidipine and at least one skin permeation enhancer.

9. A solution as claimed in claim 8 which comprises lacidipine, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

Figure 1: schematic section of a TTS according to the invention

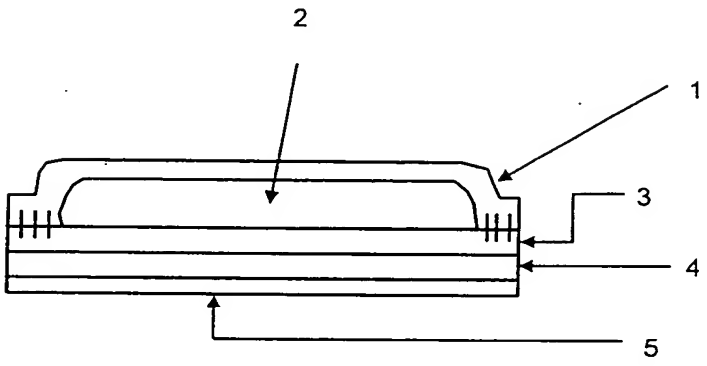

Figure 2: top view of TTS according to the invention prior to filling and sealing